Redox-Active NO_x Ligands

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Redox-Active NO_x Ligands in Palladium-Mediated Processes

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Dedicated to Prof. Anny Jutand and
Dr. C. Barry Thomas

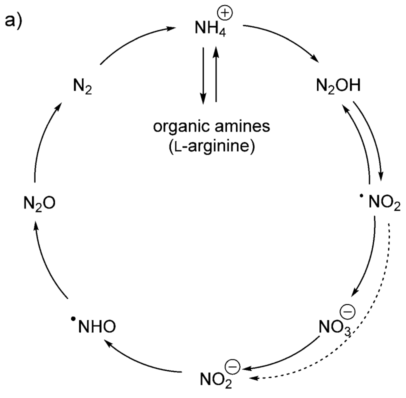
C–C coupling · oxidation · palladium · reaction mechanisms · redox reactions

This Minireview highlights the redox and non-innocent behavior of NO_x ligands ($x = 1, 2,$ or 3) in selected Pd-mediated processes, for example, alkene and aromatic oxidation processes. A focus is placed on mechanistic understanding and linking recent transformations, such as C–H bond activation/functionalization and Wacker oxidation, with previous work on the functionalization of aromatics and alkenes by Pd^{II} salts.

1. Introduction

There has been notable recent interest in the redox and non-innocent behavior of nitrate (NO_3^-) and nitrite (NO_2^-) ligands as anions in C–H bond activation/functionalization processes and Wacker-type chemistry. In the last few years, papers have been published by the research groups led by Sanford,[1] Grubbs,[2] and others. The anionic nitrate and nitrite ligands offer considerable potential as co-catalysts/oxidants in oxidative processes mediated by Pd^{II} salts, particularly when the NO_x species are redox-active under the reaction conditions. The recent findings build on fundamental work with both catalytic and stoichiometric Pd salts in alkene acetoxylation, aromatic nitration, and acetoxylation, reported by several groups as far back as in the 1960s and 1970s. This Minireview is not intended to cover all the effects of NO_x ligands (e.g. as discrete or stable anions) in Pd-catalyzed/mediated organic transformations. However, in the examples that were selected for discussion, a powerful effect of NO_x ligands has been noted, particularly where such ligands influence the redox process of a given transformation and by virtue become non-innocent participating ligands in catalysis.

In order to understand NO_x redox chemistry, it is instructive to consider the nitrogen redox cycle involving electron transfer and enzymes (depicted as a simplified cycle in Scheme 1). Several nitrogen-containing species are involved, with the nitrogen atom in various different oxidation states. It is also instructive to consider the half-reaction potentials in this respect, which are available in suitable undergraduate textbooks.[3] Typical reaction equations that can be considered useful, in the context of the chemistry described within this Minireview, are also given in Scheme 1.[4]



b)

$$Pd^0 + 2HNO_2 + 2H^+ \longrightarrow Pd^{II} + 2NO + 2H_2O$$

$$2NO + 2HNO_3 \rightleftharpoons 2NO_2 + 2HNO_2$$

$$2NO_2 + H_2O \rightleftharpoons HNO_2 + HNO_3$$

$$Pd^{II} + NO_2^- \longrightarrow [Pd(NO_2)]^+$$

$$[Pd(NO_2)]^+ + CH_2{=}CH_2 + AcOH \longrightarrow [Pd(NO)]^+ + HOCH_2CH_2OAc$$

$$[Pd(NO)]^+ + NO_2 \longrightarrow [Pd(NO_2)]^+ + NO$$

Scheme 1. a) Simplified nitrogen redox cycle. b) Selected equations describing the reactions of NO_x with Pd (higher oxidation states at Pd are not given here, but can be considered).

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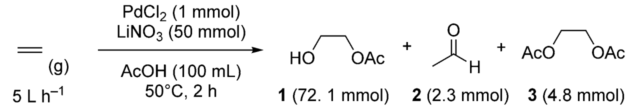
1.1. Alkene Acetoxylation and Effect of NO_2/NO_3 Anionic Ligands

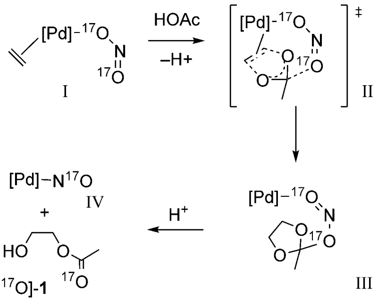
In 1968, Tamura and Yasui reported[5] the formation of ethylene glycol monoacetate (**1**, major product) by a Pd-$(OAc)_2$/$LiNO_3$-catalyzed reaction of ethylene gas in acetic acid (acetaldehyde (**2**) and ethylene glycol diacetate (**3**) were minor products; Scheme 2). The reaction was proposed to involve linkage isomerization of the Pd–NO_3 to a Pd–ONO species, as an important step in the reaction. It was not indicated in that study whether oxygen-atom transfer from $LiNO_3$ to the carbonyl group of the product occurred. The reaction led to the formation of both NO and N_2O. When O_2 was used as the terminal oxidant, NO was not detected, presumably as reoxidation to NO_x was favored under the reaction conditions that were used. Interestingly, $Cu(NO_3)_2$ and $Fe(NO_3)_3$ were active oxidants, as were $LiNO_2$ and $NaNO_2$. However, $Ba(NO_3)_2$ and KNO_3 were inactive, an outcome linked to their poorer solubility. This particular chemistry is arguably the first that took advantage of the redox-linked process involving NO_3^-, NO_2^-, NO_2, NO, and N_2O. The mechanism for the reaction of ethylene to products **1**–**3** is believed to involve a π-alkene Pd^{II} complex and NO_x linkage isomerization. The precise reaction mechanism was investigated by Yermakov et al., allowing a balanced equation in respect of **1** to be formulated [Eq. (1), Scheme 2].[6]



$$3\ C_2H_4 + 2\ LiNO_3 + 5\ AcOH \longrightarrow 3\ '\mathbf{1}' + 2\ LiOAc + 2\ NO + H_2O \qquad (1)$$

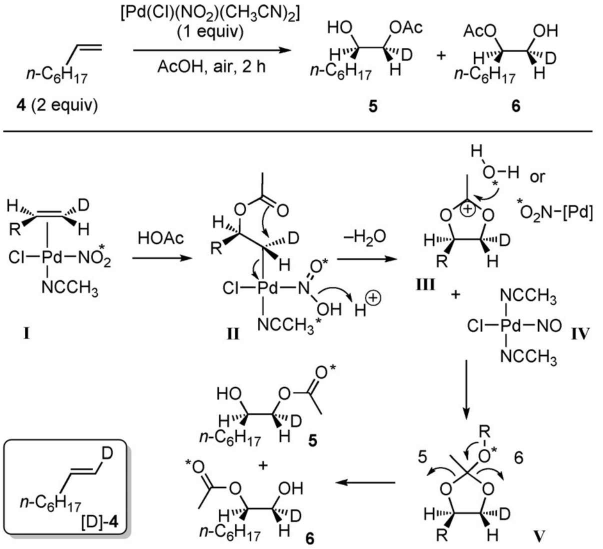
Scheme 2. $LiNO_3$/Pd^{II} salt oxidation of ethylene gas.

The mechanism was examined by the use of ^{17}O-labeled $LiN^{17}O_3$, which indicated the formation of Pd–nitrito intermediates **I**–**III**, allowing a reaction pathway to be proposed (Scheme 3).[7] The position of the ^{17}O label in the carbonyl moiety of product **1** was seen as good evidence for the proposed mechanism. The nitrito–Pd intermediate **I** reacts with a π-coordinated alkene and one molecule of acetic acid, giving transition state **II**, which releases acetyl-nitrosyl Pd intermediate **III**, and explains how the ^{17}O has been transferred from NO_2 to the acetate within the product. The reaction of **I**→**III** might be considered as having high molecularity, however there is a preorganization of both alkene and nitrite at Pd^{II} in **I** which reacts with acetic acid to give **III**, making it formally bimolecular. The formal collapse of **III** to the product ^{17}O-**1** and the oxygen-deficient Pd–NO species **IV** completes the process.



Scheme 3. Yermakov's proposed mechanism[7] for the formation of ^{17}O-**1** mediated by $Pd(OAc)_2$/$LiN^{17}O_3$ (the ligands around the Pd center or oxidation state are not specified in the original paper).

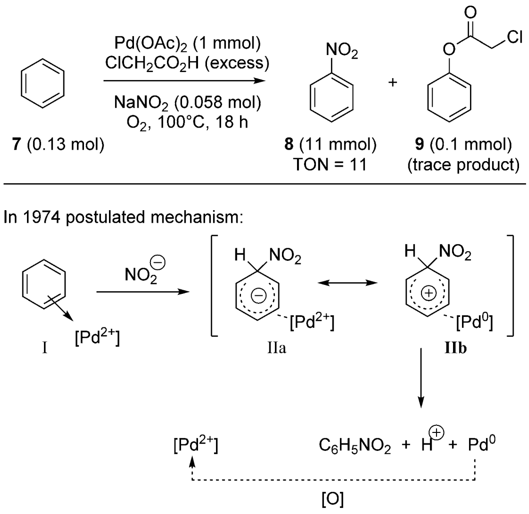
Yermakov's mechanistic proposal about the non-innocent role of nitrate and nitrite in this chemistry was further strengthened by a study by Bäckvall and Heumann,[8] involving $[Pd^{II}(Cl)(NO_2)(CH_3CN)_2]$, a catalyst used extensively in the catalytic oxidation of alkenes to epoxides, ketones, and glycol monoacetate derivatives.[9–12] Broadly speaking, terminal alkenes give rise to a 1:1 ratio of acetoxylated glycol monoacetate products **5** (anti-Markovnikov) and **6** (Markovnikov; Scheme 4). The use of (*E*)-1-deuterio-1-decene [D]-**4** as a stereochemical probe allowed the reaction path to be better defined. The study was based upon previous experimental observations from Mares and co-workers,[13] who



Scheme 4. Bäckvall–Heumann mechanism for alkene oxidation (**4**→**5**+**6**) involving nitrite anions at Pd^{II}. The * indicates the location of the oxygen and isotopic label.

Ian J. S. Fairlamb was appointed as lecturer in York in 2001, following a Ph.D. with Dr. J. M. Dickinson in Manchester (1996/9), and post-doctoral research with Prof. G. C. Lloyd-Jones in Bristol (2000/1). He was a Royal Society URF (2004/12) and promoted to full Professor in 2010. He leads a talented research group interested in catalysis, mechanism, and synthesis. Recent work includes Pd catalyst and ligand design (e.g. imidate anions and dba-Z ligands), involvement of higher-order Pd species (e.g. nanoparticles), and exploiting mechanistic understanding in purine and amino acid C–H functionalization.

carried out isotopic-labelling studies with $N^{18}O_2^-$. Coordination of **4** to Pd^{II} gives π-complex **I**, which can be attacked by AcOH to form acetoxonium intermediate **II** by a transacetoxylation reaction. The neighboring acetate group is then able to facilitate oxidative cleavage of the Pd−C bond with inversion, affording a five-membered cyclic cationic intermediate **III**, releasing $H_2{}^{18}O$ and nitrosyl–Pd intermediate **IV**. Recombination of the ^{18}O-containing species, either $H_2{}^{18}O$ or [Pd]-$N^{18}O_2$, with **III** then affords **V**, which can rearrange through two pathways to give either regioisomeric product **5** (anti-Markovnikov) or **6** (Markovnikov). The authors commented that labeled water does not exchange with acetic acid under the reaction conditions, but a tight ion-pair interaction between an anionic [Pd]-$N^{18}O_2$ species with **III** could better explain the re-association of the ^{18}O label (*) with the organic product. It is interesting to note that the proposed mechanism shares a similarity with Woodward's *cis*-hydroxylation reaction.[14]



Scheme 5. Catalytic nitration of benzene **7** by $Pd(OAc)_2/NaNO_2$ catalyst system under oxygen to give **8** and **9** (TON = turnover number of the Pd^{II} catalyst).

1.2. Aromatic Acetoxylation and Nitration

There was significant effort in the 1970s directed toward utilizing Pd^{II} salts in the nitration and acetoxylation of aromatic compounds. Ichikawa and co-workers[15] uncovered nitroaromatic compounds as by-products in the reactions of benzene, toluene, xylenes, and mesitylene with $Pd(NO_3)_2$ in acetic acid at 90–115 °C. Henry reported that addition of $NaNO_2$ or $NaNO_3$ to $Pd(OAc)_2$-mediated nitration of benzene to give $C_6H_5NO_2$.[16] Tisue and Downs[17] noted the formation of $C_6H_5NO_2$ and C_6H_5OAc on treatment of colloidal Pd (catalytic) with either $NaNO_2$, NO_2, or a combination of NO/O_2 in the presence of benzene in acetic acid at 100 °C. Following these early observations, Norman, Parr, and Thomas[18] developed a catalytically competent system for aromatic nitration, which also led on to other aromatic oxidations beyond the scope of this Minireview.[19] An example is shown in Scheme 5 (**7**→**8** + **9**) using chloroacetic acid, which is highly selective for $C_6H_5NO_2$ (**8**) and proceeds with a catalyst turnover number of 11. In the absence of $NaNO_2$, but using $Pd(NO_3)_2$ as the catalyst, the dominant reaction involves formation of the acetoxylation product **9**.

Norman's group in York postulated a mechanism based on the unusual observation that both toluene and chlorobenzene exhibit *para* selectivity (note: NO_2^+ was discounted as a reagent, as the partial selectivities between toluene and chlorobenzene were not in agreement with traditional nitronium ion chemistry). The first step involves π complexation of the aromatic ring with Pd^{II}, giving Pd^{II} π complex **I**. Attack of the π complex with NO_2^- affords intermediate **IIa**, which is stabilized by Pd^{II}. A canonical form of **IIa** is **IIb**, in which the aromatic electrons have been transferred to give Pd^0. Loss of H^+ and extrusion of Pd^0 (observed under the reaction conditions) liberates $C_6H_5NO_2$ (**8**), explaining the need for an oxidant to regenerate Pd^{II} to close the catalytic cycle.

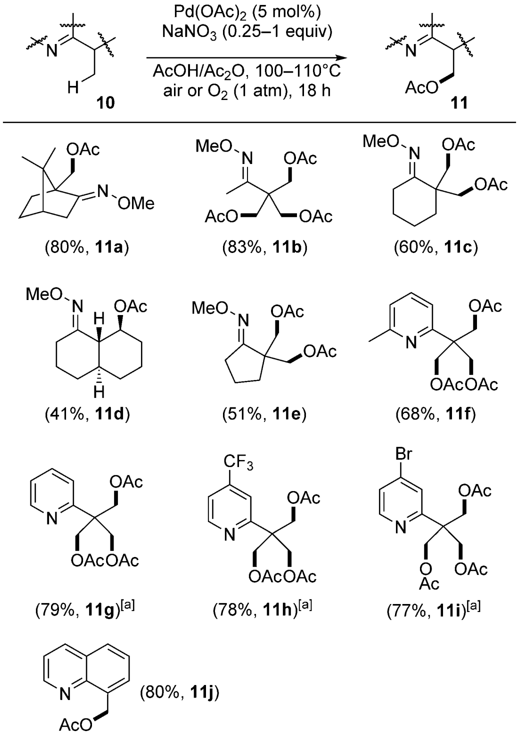
Aromatic acetoxylation has recently attracted attention by the Stahl group,[20] who reported that the Pd-catalyzed aerobic oxidation of benzene in acetic acid (under 1 atm O_2) affords acetoxybenzene with catalyst turnover numbers of up to 136, and with high selectivity over nitrobenzene (up to 40:1). The process takes advantage of a redox-active NO_x species, and the best results were obtained using fuming HNO_3 in substoichiometric quantities (e.g. 30 mol %); other NO_2 sources were also tested and found to be less selective. The amounts of nitrobenzene that was formed increased for other NO_2 sources, indicating N coordination to Pd within the catalytic cycle, although Norman's mechanism (see above) should also be taken into account (see also Section 3). Recent studies on the catalytic nitration of C−H bonds bearing appropriate directing groups, is covered in further detail in Section 4.

2. Redox-Active and Non-Innocent NO_x Anions

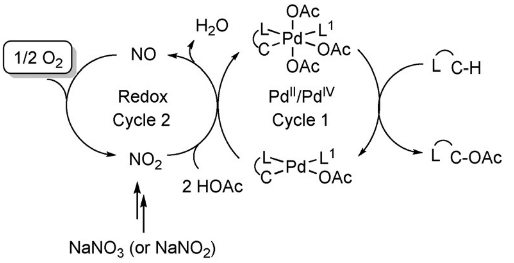
2.1. C(sp^3)−H Bond Activation

In 2012, Sanford and co-workers reported a methodology for the acetoxylation of non-activated C(sp^3)−H bonds (Scheme 6).[1] Exemplar reactions include substrates containing oxime ether (**11a–e**) and pyridine-type (**11 f–j**) directing groups. In all cases, the nitrogen atom plays the role of a directing group at Pd. Typical reactions employ $Pd(OAc)_2$ as a catalyst, $NaNO_3$ as a co-catalyst, and dioxygen as the terminal oxidant, in a solvent combination of acetic acid and acetic anhydride (typically 5:1, *v*/*v*). $NaNO_3$ has a remarkable effect on catalyst efficacy. Indeed, NO was detected under catalytic conditions, and it was proposed that the redox activity of the nitrate anion was crucial to the success of this chemistry. It was also demonstrated that $NaNO_2$ can play a similar activating role, having a marginally lower activity compared with $NaNO_3$ (shown for one substrate, **10a**→**11a**, Scheme 6).

Sanford and co-workers[1] suggested that the acetoxylated product **11** derives from acetic acid (solvent) and not O_2, which was confirmed by experiments with ^{18}O-labeled



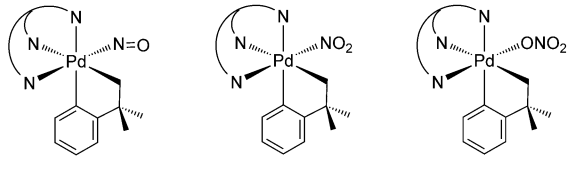
Scheme 6. Substrate scope in Sanford's C(sp^3)−H bond acetoxylation.[1] The bonds highlighted in bold show the position of the new acetoxy group. [a] 4 Å molecular sieves were added.



Scheme 7. A general mechanism for the C(sp^3)−H bond functionalization, as proposed by Sanford and co-workers[1] (the stereochemistry at each Pd center is not indicated, as it is unknown).

dioxygen, leading to the mechanistic proposal outlined in Scheme 7 (note: drawn as in the original paper, except L^1 has been included here to fill the vacant site within the octahedral Pd^{IV} species). The mechanism consists of two cycles. Cycle 1 involves the organic substrate and Pd^{II} and Pd^{IV} species. Cycle 2, which interfaces with cycle 1 through an unknown mechanism, involves both NO and NO$_2$ species and two molecules of acetic acid. The involvement of Ac$_2$O, present in excess with respect to the starting material **10**, was not explicitly stated in the paper, but presumably it acts to sequester the H$_2$O released in the final step of the interfacing catalytic cycles.

Sanford suggested that the ligand set at Pd was not defined, and that N-containing ligands could be present. This point is supported by the fact that Pd^{IV} species, containing NO as a ligand, have been reported previously by Cámpora, Palma, and co-workers (depicted as "N ~ N ~ N-Pd-NO", complex **12** in Scheme 8). Complex **12** was formed by the reaction of an in situ generated anionic Pd^{II} salt with diazald (*N*-nitroso-*N*-methyl-*p*-toluenesulfonamide).[21] Oxidation of **12** with O$_2$ in toluene gave "N ~ N ~ N-Pd-NO$_3$" (**14**) in approximately 50% yield, a species which was described as a non-electrolyte. While no direct evidence was gained for "N ~ N ~ N-Pd-NO$_2$" (**13**) being formed as an intermediate in the reaction, its independent synthesis was accomplished by an alternative synthetic route. The study suggests that **12** and **14** could form a redox cycle in the presence of O$_2$.



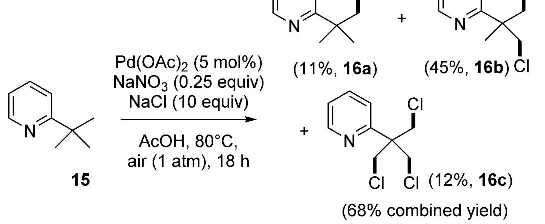
12, 'N~N~N-Pd-NO' **13**, 'N~N~N-Pd-NO$_2$' **14**, 'N~N~N-Pd-NO$_3$'

Scheme 8. Nitrosyl, nitro, and nitrato complexes of Pd^{IV} (N ~ N ~ N = tris(pyrazolyl)borate ligand), reported by Cámpora, Palma, and co-workers.[21]

The study by Cámpora et al.[21] is central to understanding Sanford's results, as the O$_2$ plays the role of terminal oxidant in the reaction, in which NaNO$_3$ is present in substoichiometric amounts. It was also noted that in the absence of O$_2$ (under N$_2$ atmosphere), the turnover was linked to the quantity of NaNO$_3$ that was present.

While no further mechanistic details were presented in Sanford's study,[1] it is of interest to consider the postulated mechanism. For example, do cycles 1 and 2 (Scheme 7) occur independent of each other, or is Pd somehow involved in both cycles? NO$_x$ are known to be active ligands at Pd^{II} in other complexes, as outlined later in this Minireview, therefore their role as ligands at Pd cannot be ruled out.

In their efforts toward expanding the scope of the methodology, Sanford and co-workers obtained a mixture of mono- (**16a**), di- (**16b**, major), and trichlorinated (**16c**) products from the Pd(OAc)$_2$/NaNO$_3$-mediated aerobic oxidation of 2-*tert*-butylpyridine **15** (Scheme 9).[1] Further optimization of this reaction was difficult. It is interesting to note that when Yermakov et al. examined the role of LiClO$_3$, LiBrO$_3$, and LiIO$_3$ as oxidants in the formation of ethylene glycol monoacetate (**1**), low concentrations of LiCl acceler-

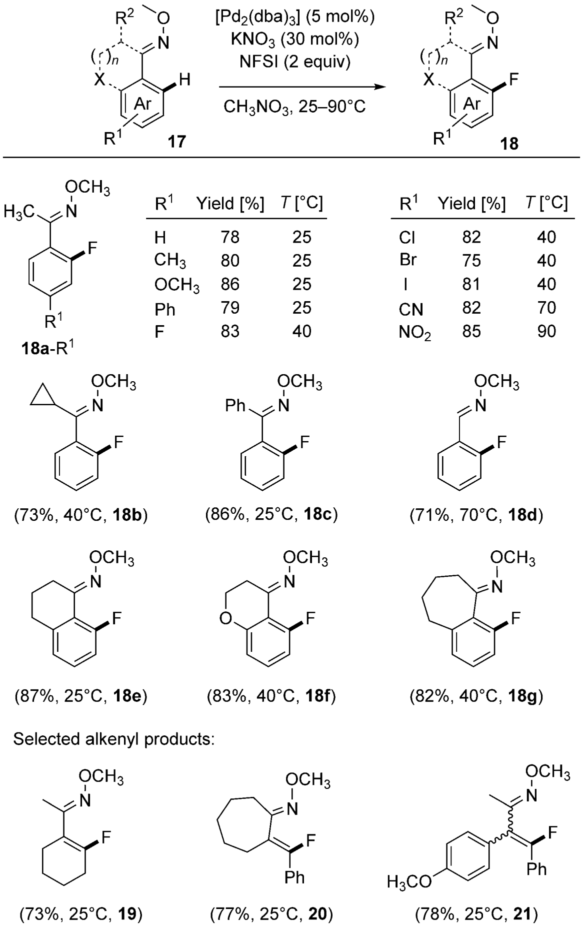


Scheme 9. Preliminary chlorination reaction using an excess of NaCl, reported by Sanford and co-workers.[1] The bond highlighted in bold shows the position of the new chloro group.

ated the reaction, whereas higher concentrations inhibited the reaction.[22] While a different type of reaction, Yermakov's earlier work points to excess salt being a potential issue for this type of oxidative Pd-catalyzed process.

In 2014, Xu and co-workers[23] demonstrated that MNO_3 (M = K or Ag) can act as a co-catalyst in catalytic C−H bond fluorinations. Using an *N*-methyl oxime group as a directing group at Pd, the reaction worked well for a series of aryl and alkenyl substrates using *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent and $[Pd_2(dba)_3]$ (dba = *E*,*E*-dibenzylidene acetone) as the catalyst. This result is unusual. If we presume an oxidative process (presence of "F^+"), then the active catalyst species are likely to be in higher oxidation states, for example, Pd^{II}–Pd^{IV}.[24] Therefore, the Pd^0 precatalyst needs to be oxidized first to an active Pd^{II} form.

The general reaction conditions, including a summary of the study on the substrate scope, are collated in Scheme 10. The reaction worked well for a range of substituted acetophenone *O*-methyl oximes (**18a**-R^1), and also for substrates bearing a cyclopropyl substituent and ring-expanded derivatives (examples **18b–g**). A few alkenyl substrates were also tested, with the fluorinated products (**19**–**21**) formed in good yields at 25 °C.



R^1	Yield [%]	*T* [°C]	R^1	Yield [%]	*T* [°C]
H	78	25	Cl	82	40
CH_3	80	25	Br	75	40
OCH_3	86	25	I	81	40
Ph	79	25	CN	82	70
F	83	40	NO_2	85	90

Scheme 10. Substrate scope of the C(sp^2)−H bond fluorination described by Xu et al. (selected examples). The bonds highlighted in bold indicate the positions of the newly attached fluoro group.

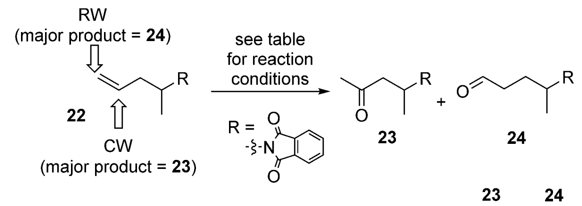
A selected reaction of **17a**-H to give **18a**-H was successfully scaled-up to 10 mmol. During the optimization of the reaction conditions, several MNO_3 salts were evaluated and led to different outcomes. Product selectivity emerged as a particular issue, specifically as a competing difluorination occurred as a secondary process. Most interesting was the finding that $Pd(NO_3)_2{\cdot}2H_2O$ was less selective than the $[Pd_2(dba)_3]/AgNO_3$ catalyst combination. A role for the dba ligand was not discussed in detail, although it is well established that dba can be non-innocent (in a positive and negative sense) in cross-coupling catalysis, as shown by Amatore and Jutand.[25] It is known that certain types of dba-Z ligands can influence the reactivity of Pd^{II} centers,[26,27] although evidence for an interaction between dba/dba-Z ligands and either Pd^{III} or Pd^{IV} is not yet available.[24,27]

In recent years, ESI-MS has been used by several groups to probe for species that reside in solution under working reaction conditions.[28] Xu and co-workers[23] were able to utilize this technique to detect Pd species present under their reaction conditions, although none of the characterized Pd intermediates contained NO_x.

2.2. Catalyst-Controlled Wacker Oxidations of Alkenes

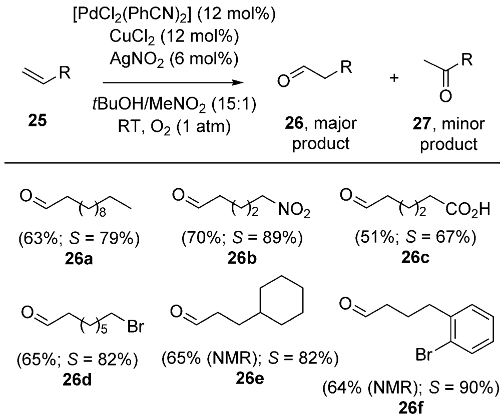
Grubbs and co-workers[2a] noted that MNO_2 salts could be used in the Wacker oxidation of terminal alkenes to give aldehydes and ketones. Classically, the major product of a Wacker oxidation mediated by Pd/Cu under an O_2 atmosphere is the ketone, the formation of which is substrate-controlled (i.e. the Markovnikov product). A leading example is shown in Scheme 11. The reaction of **22**→**23** + **24** at room temperature gives ketone **23** selectively. Under slightly different conditions, the presence of nitrite anions (in the form of $AgNO_2$) results in the formation of aldehyde **24** as the major product. The formation of aldehyde **24** can be explained by a catalyst-controlled variant of the Wacker oxidation reaction, which is referred to as the reverse Wacker reaction to allow differentiation in the substrate-controlled process.

Grubbs' catalyst-controlled synthetic methodology facilitates the functionalization of challenging aliphatic substrates (see Scheme 12 for selected examples). The lack of interfer-



	23	24
CW: $PdCl_2$ (cat.), CuCl (1 equiv), DMF/H_2O (7:1), RT, O_2 (1 atm)	85	15
RW: $[PdCl_2(PhCN)_2]$ (12 mol%), $CuCl_2$ (12 mol%), $AgNO_2$ (6 mol%), *t*BuOH/$MeNO_2$ (15:1), RT, O_2 (1 atm)	10	90

Scheme 11. Mechanistic dichotomy observed by Grubbs and co-workers[2a] in the Wacker oxidation of terminal alkenes. RW = reverse Wacker reaction, CW = classic Wacker reaction.

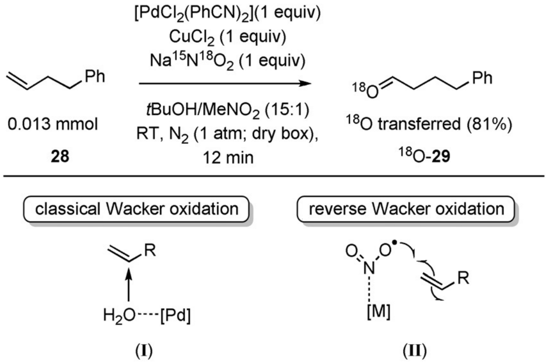


Scheme 12. Substrate scope in catalyst-controlled Wacker oxidation reactions described by Grubbs (selected examples).[2] Yields of isolated aldehyde are given, unless otherwise specified; *S* = selectivity for aldehyde according to ^{1}H NMR spectroscopic analysis.

ence from allylic and homoallylic functionalities indicates that the synthetic methodology holds future promise for application in more structurally complex systems, for example, natural products.

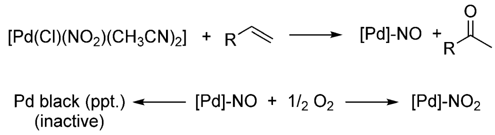
The mechanism of the catalyst-controlled Wacker oxidation deserves some comments; the mechanism proposed by Grubbs is shown in Scheme 13. Use of ^{18}O-labeled nitrite anion (from $Na^{15}N^{18}O_2$, 90% ^{18}O and 95% ^{15}N), once again proved useful, as seen earlier in Yermakov's studies.[7] Reaction of 4-phenyl-1-butene (**28**) with stoichiometric amounts of $Na^{15}N^{18}O_2$, $[PdCl_2(PhCN)_2]$, and anhydrous $CuCl_2$, for 12 min at room temperature (reaction quenched by addition of dry pyridine and cooling to −78 °C), showed that the ^{18}O label was effectively incorporated into the aldehyde product **29** (81%). It was suggested that incomplete ^{18}O incorporation (≈9%) was likely due to the presence of adventitious water (appropriate controls were in place to minimize oxygen exchange via a hemiacetal species).

It was proposed that an unusual catalytic manifold and mechanism could be operational in the reverse Wacker reaction. A proposed radical model partly explains the anti-Markovnikov selectivity, operating via a metal species such as **II** (Scheme 13). Here, a nitrite ligand at a metal center (M = Pd/Cu) can attack the terminal position of the alkene substrate, where the developing radical is stabilized by a secondary radical intermediate. The transfer of the ^{18}O label from the metal to the substrate is in keeping with Yermakov's observations at Pd^{II}, as described in Section 1.1.[7] In another follow-up paper, Grubbs reported an aldehyde-selective oxidation that enabled the rapid, enantioselective synthesis of the pharmaceutical agent, atomoxetine.[2b]



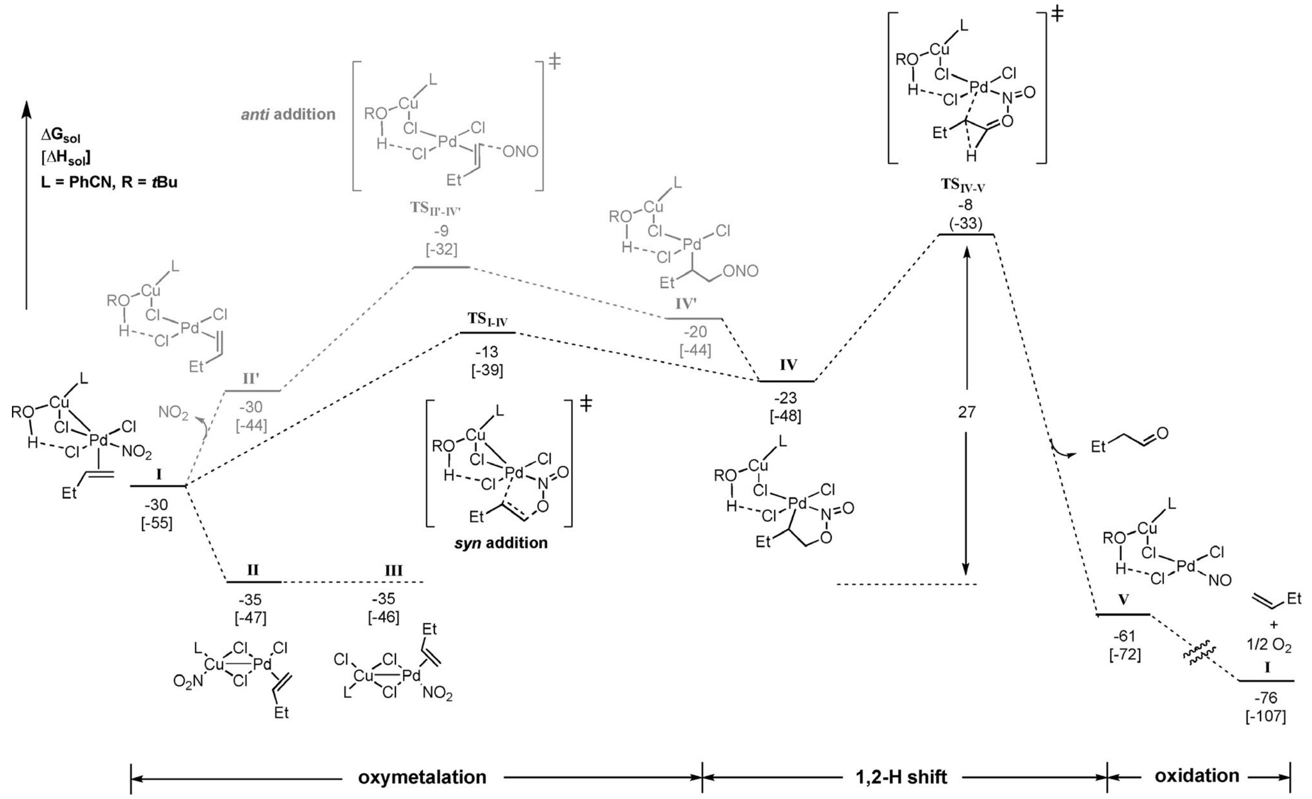
Scheme 13. Mechanism[2a] proposed by Grubbs for the catalyst-controlled Wacker oxidation of terminal alkenes.

Prior influential work by Feringa showed that $[Pd^{II}(Cl)(NO_2)(CH_3CN)_2]$ (also see Section 1.1 for the use of this catalyst) and $CuCl_2$ catalyzed the Wacker oxidation of terminal alkenes, which was modestly regioselective for aldehydes (relatively low yields were recorded, with ca. 20% being the highest).[29] In Feringa's case, and perhaps more important in terms of the mechanism explaining the observed regioselectivity, was the proposal of a *t*BuOH-ligated heterobimetallic Pd/Cu catalyst species, which nicely links to the subsequent computational work recently published (see below). Wenzel later exemplified aerobic NO_2 turnover using $[Pd^{II}(Cl)(NO_2)(CH_3CN)_2]$ in two oxidative processes:[30] a) Pd-catalyzed reaction of alkenes to ketones, and b) oxydehydrogenation of ketones and aldehydes to α,β-unsaturated compounds. It was proposed that the reduced [Pd]-NO species is formed alongside the ketone product in the alkene oxidation. Reoxidation of [Pd]-NO can then occur with molecular O_2 to regenerate the active catalyst, depicted generally as [Pd]-NO_2 (Scheme 14). Catalyst deactivation was also observed in Wenzel's chemistry, consistent with the formation of an in active Pd black precipitate.



Scheme 14. Aerobic NO_2 turnover at Pd in the catalytic oxidation of alkenes using $[Pd(Cl)(NO_2)(CH_3CN)_2]$ catalysts. ppt. = precipitate.

Given the complexity of reaction mixture required for the reverse Wacker reaction, described by Grubbs (i.e. required for multiple reagents/catalysts/co-catalysts/solvents),[2a] it is difficult to study the mechanism by experiment, although not insurmountable. This challenge led Yu, Fu, and co-workers[31] to first examine the mechanistic possibilities using a computational approach. The main aim of the study was to decipher the observed aldehyde selectivity by density functional theory (DFT) methods. The authors considered two oxymetalation pathways, which differed in the mode of addition of the nitrite to the alkene, occurring in either a *syn* or *anti* manner (Scheme 15). They rather stoically considered a variety of possibilities, including active species as monomeric Pd, bimetallic Pd–Pd, and two heterometallic Pd–Cu and Pd–Ag species. Kinetically, the *syn* mode of addition of nitrite anion to the metal center was most favored. Of the different metal species, the heterobimetallic Pd–Cu species was selected as the preferred system. There is a nice synergy here with Feringa's earlier studies,[29] in which the solvent, *t*BuOH,



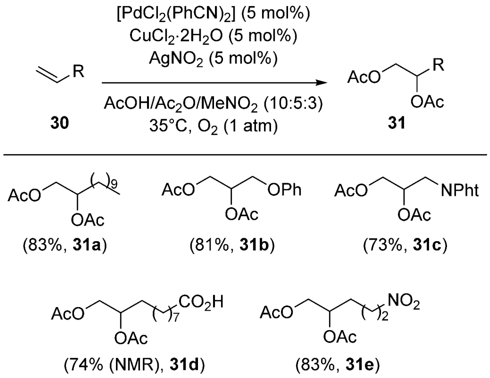
Scheme 15. Mechanistic proposal to explain the reverse Wacker oxidation process, as predicted by DFT methods.[31] The kinetically preferred pathway is **I-TS$_{I–IV}$-IV** (*syn* addition); the *anti*-addition pathway is **I-II′-TS$_{II′–IV′}$-IV′-IV**, shown in grey.

was suggested to play a nonspectator role, in addition to the nitrite anion.

In terms of the mechanism that was proposed, oxymetalation of model alkene substrate, 1-butene, occurs from **I** through the *syn* addition of NO_2 at the Pd center to a terminal η^2-alkene carbon atom via transition state **TS$_{I–IV}$**, giving cyclopalladated intermediate **IV**. The alternative pathway (**I**→**II′**→**TS$_{II′–IV′}$**→**IV′**→**IV**, shaded in grey in Scheme 15) was kinetically less favorable than the *syn* addition pathway. The aldehyde formation step involves a 1,2-H shift mechanism on *t*BuOH-ligated Pd–Cu complexes from **IV** to **V**, via **TS$_{IV-V}$**. An alternative β-H elimination pathway was ruled out on the basis that it was too high in energy. This particular step is intriguing and led the authors to examine the spin-density population connecting **IV** and **V**, which shows that a radical 1,2-H shift on the oxygenated alkene is promoted.

Experimental support for the reaction mechanism proposed by DFT methods is needed, but it ought to be possible to establish the reaction order with regard to Pd and Cu for these reactions, providing potential evidence for the involvement of bimetallic Pd–Cu species, as suggested by computation. The authors did not examine the "M-NO_2"→"M-ONO" linkage isomerization explicitly. Concerning the nature of the Pd–Cu species, which were proposed as active species in this chemistry, it is interesting to note that similar bimetallic Pd–Cu species have been proposed for Sonogashira cross-couplings by Vasella and co-workers.[32]

During late 2014, Grubbs reported the aerobic Pd-catalyzed dioxygenation of alkenes **30** to give diacetoxylation products **31**, enabled by catalytic nitrite anions (Scheme 16).[33] Here, the authors suggested that NO_2, which could form from nitrite under the reaction conditions, was a potential intermediate within the catalytic cycle. ^{18}O-labeling experiments showed that both oxygen atoms in the diacetoxylated products derive from one molecule of acetic acid. The nitrite anion was described as an electron-transfer mediator and high-energy stoichiometric oxidant in these reactions. As AcOH and Ac_2O are present in large quantities, it is more difficult to monitor the destination of an ^{18}O label from $AgNO_2$ in these reactions. The role of the Ac_2O was not discussed, but as with Sanford's chemistry, it can act to sequester the H_2O formed under the reaction conditions.



Scheme 16. Substrate scope in the diacetoxylation of terminal alkenes (selected examples). Pht = phthaloyl.[33]

3. Coordination of NO$_x$ Ligands to Pd and Contamination of Pd Catalysts

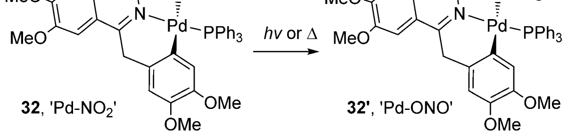
The research findings highlighted above raise questions about the potential interaction of NO$_x$ ligands at Pd. Similar questions have been asked about the catalytic behavior of metalloporphyrins containing NO$_x$ ligands, in which linkage isomerization plays a key role in the behavior of NO$_x$ ligands at the metal center.[34]

3.1. Pd–NO$_x$ Coordination and the "Pd–NO$_2$"→"Pd–ONO" Linkage Isomerization

The coordination of nitrite and nitrate ligands to Pd has been widely investigated over the years.[35] Nitrate ligands coordinate through oxygen to Pd^{II} to form neutral complexes, for example, [Pd(L)$_2$(NO$_3$)$_2$], and cationic complexes, for example, [Pd(L)$_n$X]$^+$NO$_3^-$, of which many are ubiquitous.[36] Nitrite ligands can coordinate Pd through nitrogen or oxygen. It should be noted that several M-NO$_2$ coordination modes are known, which usually stabilize binuclear metal coordination environments, with the NO$_2$ acting as a bridging ligand.[37]

Linkage isomerization involving M-NO$_2$ is well established for transition metals,[38] the effect of which in terms of applied homogeneous catalysis processes has not been investigated to a great extent. With regard to stoichiometry, my group presented the first well-characterized "Pd–NO$_2$"→"Pd–ONO" linkage isomerization[39] for a Pd^{II} complex, namely palladacycle **32**, formed by cyclopalladation of the natural product papaverine,[40] in the solid-state[41] (Scheme 17). The linkage isomerization process can either be thermally or photochemically induced, and results in the "ON=O" group being *endo* to the Pd center (as shown in **32′**).[42] The photochemical behavior associated with the "Pd–NO$_2$" **32**→"Pd–ONO" **32′** linkage isomerization confirms that any chemistry involving NO$_2$ ligands at Pd^{II} can be influenced by light. Moreover, NO$_2$ can act as a ligand within the coordination sphere of a cyclopalladated system, that is, commensurate with the types of palladacyclic intermediates that have been proposed in catalytic C–H bond functionalization processes, for example, those described by Sanford and co-workers[1] (note that in our case the carbon atom connected to Pd^{II} is sp^2- rather than sp^3-hybridized).

Structurally less complicated systems such as [Pd(L)$_2$(NO$_2$)$_2$], in which L = PPh$_3$ and AsPh$_3$, also exhibit photochemically induced "Pd–NO$_2$"→"Pd–ONO" linkage isomerization in the solid state.[43] In such complexes, thermally induced "Pd–NO$_2$"→"Pd–ONO" linkage isomerization occurs readily in solution.[44]

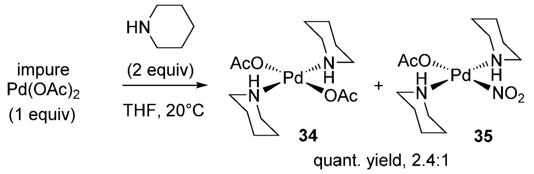


Scheme 17. "Pd–NO$_2$"→"Pd–ONO" linkage isomerization in a palladacycle containing a Pd^{II} center.

With regard to catalysis, the "Pd–NO$_2$"→"Pd–ONO" linkage isomerization described above could influence secondary processes, such as alkene isomerization. This proposal is supported by the Pd–NO$_2$ interaction with π-coordinated alkenyl substrates that are required for the reverse Wacker oxidation (see Section 2.2).[2,31]

3.2. Pd(OAc)$_2$ Contamination with NO$_x$ Ligands

My group's research activities in this area, described in Section 3.1, evolved from observations made during synthetic and mechanistic work on the catalytic direct arylation of 2′-deoxyadenosine (see Scheme 19) using *trans*-[Pd(OAc)$_2$(piperidine)$_2$] (**34**) as the precatalyst (which is catalytically more active than Pd(OAc)$_2$).[45] Nitrite impurities derived from Pd(OAc)$_2$ were appearing in stoichiometric reactions with piperidine, to give both **34** and *trans*-[Pd(OAc)(NO$_2$)(piperidine)$_2$] (**35**) complexes (Scheme 18). We eventually deduced that [Pd$_3$(OAc)$_5$(NO$_2$)] was the source of the nitrite anion for the reaction (see Scheme 18 and Figure 1). In the same way, we could also elucidate the origin of the mysterious nitrite ligand that appeared in papaverine-derived palladacycle **32**, the synthesis of which was originally reported by Nonoyama.[40]



Scheme 18. Nitrite impurities in Pd(OAc)$_2$, for example, [Pd$_3$(OAc)$_5$NO$_2$], appear in products resulting from the reaction with piperidine to give expected complex **34** and unexpected complex **35**.[39]

At this point in the discussion it is pertinent to pass comment on the precise structure of Pd(OAc)$_2$, as structural proposals have varied from dimers, amorphous polymeric forms, to trimeric Pd clusters. It is generally agreed that crystalline Pd(OAc)$_2$ is more precisely [Pd$_3$(OAc)$_6$]; Figure 1 shows an X-ray structure of a single crystal of [Pd$_3$(OAc)$_6$], which was recently solved by my group and exhibits the required D_{3h} symmetry.[46] [Pd$_3$(OAc)$_6$] can exchange ligands quite readily, for example with nitrite anion contaminants to give [Pd$_3$(OAc)$_5$NO$_2$], or with other anionic ligands (X) to give complexes of the type [Pd$_3$(OAc)$_5$X]. Protic two-electron donor ligands[47] also interact with and influence the decomposition of this common Pd^{II} catalyst and precatalyst.

In order to gain an insight into the extent of nitrite contaminants in commercial sources of Pd(OAc)$_2$, we randomly collected a number of batches (from various suppliers) from across the different research groups at the Department of Chemistry at York (Figure 2). [Pd$_3$(OAc)$_5$NO$_2$] was found as a contaminant in every batch, with the exception of "high-purity Pd(OAc)$_2$", as indicated by a given supplier.

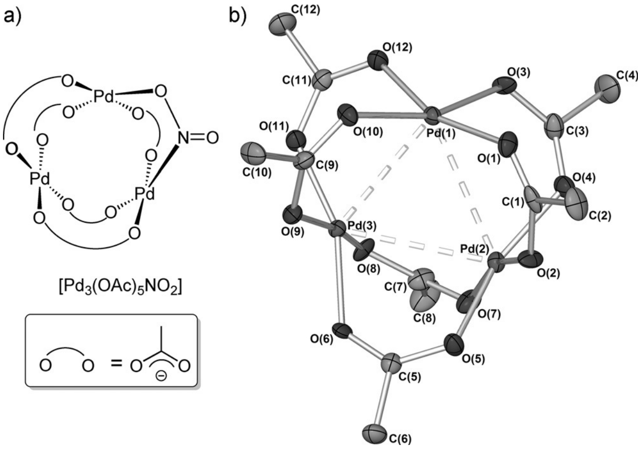


Figure 1. a) Nitrite adduct of $[Pd_3(OAc)_5NO_2]$. b) Single-crystal X-ray structure of $[Pd_3(OAc)_6{\cdot}0.2\,H_2O]$ (the hydrogen atoms of H_2O have been omitted for clarity; acetate disorder was observed, but is not shown, thermal ellipsoids at 50% probability).

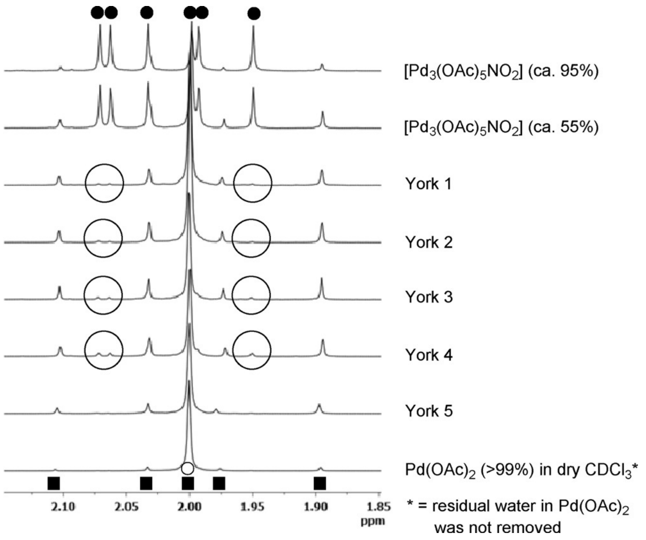
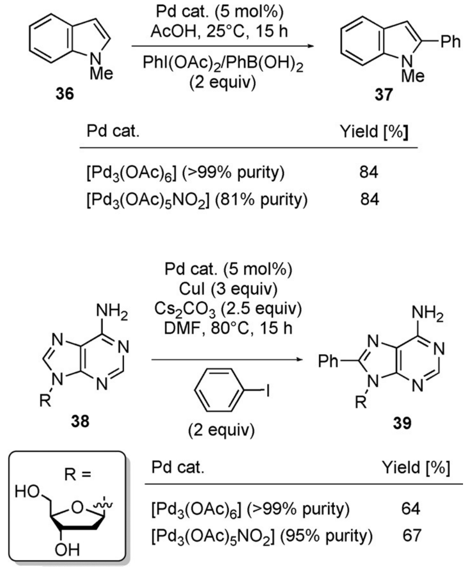


Figure 2. ^{1}H NMR spectra of various commercial batches of "Pd-$(OAc)_2$" found in the Chemistry Laboratories at the University of York. The ^{1}H NMR spectra were run using reagent grade "wet" $CDCl_3$ unless otherwise specified. The black circles highlight trace $[Pd_3(OAc)_5NO_2]$. For reference purposes, ^{1}H NMR spectra of $[Pd_3(OAc)_5NO_2]$ (ca. 95% and 55% purity materials) and pure $Pd(OAc)_2$ (open circle) in dry $CDCl_3$ are included; $[Pd_3(OAc)_6H_2O]$ is shown by black squares). Adapted from I. J. S. Fairlamb et al., *Chem. Sci.* **2012**, *3*, 1656–1661. Reproduced with permission of The Royal Society of Chemistry.

The $[Pd_3(OAc)_5NO_2]$ derives from the industrial synthesis of $[Pd_3(OAc)_6]$ from Pd^{II} salts and HNO_3. Cotton and co-workers suggested that the unsatisfactory removal of NO_x gases explains the formation of $[Pd_3(OAc)_5NO_2]$. It was suggested that the issue could be overcome effectively by bubbling N_2 through the reaction solutions.[48] However, Stolyarov et al. questioned this hypothesis,[49] providing experimental evidence that showed a relatively high nitrogen content in "$Pd(OAc)_2$" treated with this method, even following prolonged bubbling of N_2 through reaction solutions. As an important practical aside, Stolyarov et al. proposed that the best method for preparing crystalline $[Pd_3(OAc)_6]$ was by reacting $Pd(NO_3)_2{\cdot}2\,H_2O$ with $NaOAc{\cdot}3H_2O$ in aqueous acetic acid at room temperature, which gives $[Pd_3(OAc)_6]$ in 80% yield and with more than 99.9% purity. Other synthetic methods led to the formation of cyanide-containing Pd clusters, for example, $[Pd_3(OAc)_5CN]$ or $[Pd_4(OAc)_7CN]$.

Given the context of the work described above, the nitrite contaminants could be affecting catalyst efficacy in a number of systems, in the same way that impurities in $[Pd_2(dba)_3]$ are thought to influence Pd-mediated processes.[50,51] It is also pertinent to mention the recent interesting findings of Bedford et al.[52] concerning the facile hydrolysis and alcoholysis of $[Pd_3(OAc)_6]$ to give $[Pd_3(\mu^2\text{-}OH)(OAc)_5]$ and $[Pd_3(\mu^2\text{-}OH)(OAc)_5]$, respectively, of potential relevance to Wacker oxidation reactions.

We examined two exemplary C(sp^2)−H bond functionalization reactions[39] in view of uncovering an effect of the nitrite contaminant in "$Pd(OAc)_2$" (Scheme 19). The first reaction was reported by Sanford and co-workers for the arylation of *N*-methylindole (**36**→**37**).[53] The second reaction was reported by our group for the arylation of 2′-deoxyadenosine (**38**→**39**).[45] In both cases, there was remarkably no effect of the nitrite anion on the product yield. Given the large number of reports on the use of $Pd(OAc)_2$, the effect of the impurities can perhaps be considered to be small. However, impurities in $Pd(OAc)_2$ might influence kinetic analyses.



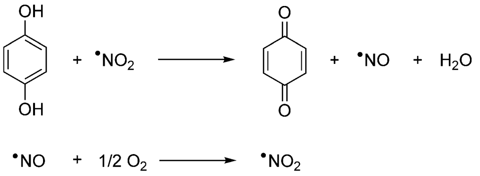
Pd cat.	Yield [%]
$[Pd_3(OAc)_6]$ (>99% purity)	84
$[Pd_3(OAc)_5NO_2]$ (81% purity)	84

Pd cat.	Yield [%]
$[Pd_3(OAc)_6]$ (>99% purity)	64
$[Pd_3(OAc)_5NO_2]$ (95% purity)	67

Scheme 19. Effect of $[Pd(OAc)_5NO_2]$ versus $[Pd_3(OAc)_6]$ in the direct arylation of *N*-methylindole (**36**→**37**) and 2′-deoxyadenosine (**38**→**39**).

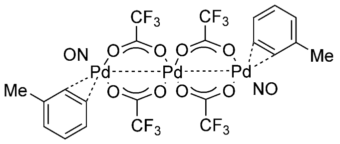
The catalytic oxidation of methane and other alkanes (to alcohols or esters) with transition metals is a reaction of great interest and considerably challenging.[54] Early examples include methane oxidation to methyl trifluoroacetic acetate using $Pd(OAc)_2$ in trifluoroacetic acid at 56–70 atm and 80 °C (taking up to 4 days to give a yield of 60%).[55–58] In 1990, Moiseev and co-workers reported that they could not reproduce the reaction.[59] They explained the anomaly, stating “unknown admixtures in the reagents are presumed to be responsible for the difference between our results and those cited”. Indeed, Stolyarov et al. followed up on this comment in a later report,[49] stating that the reaction could not be reproduced with pure $[Pd_3(OAc)_6]$, and inferring that $[Pd_3(OAc)_5NO_2]$ was responsible[60] for the reported reaction.[55,56] The function and role of the nitrite ligand in the catalytic oxidation of methane is unclear, but arguably the observation gives an indication for the future direction of catalyst design for alkane C–H bond oxidation reactions, and other related organic substrates.

Remarkably, Bao et al. reported[61] that the combination of three redox couples involving Pd^{II}/Pd^{0}, quinone/hydroquinone, and NO_2/NO (derived from $NaNO_2$) in CF_3COOH enabled the aerobic oxidation of methane at 80 °C, with a turnover of around $0.7\ h^{-1}$. The authors suggested that the catalytic process is reminiscent of biological oxidation processes, in which the Pd^{II} initiates an electron-transfer chain that carries the electrons from methane to O_2. The use of quinone/hydroquinone as a redox couple with NO_x chemistry is an interesting one, considering the equations outlined in Scheme 20, especially in the context of other C–H bond functionalization processes.



Scheme 20. Bao’s triple redox chemistry in the context of the aerobic oxidation of methane (the radicals have been added to NO and NO_2 as a modification to the original reported scheme).

Lastly, Podobedov et al. reported the transformation of benzene and toluene into biphenyls, diaryl amines, and carbazoles from a linear Pd_3 cluster containing NO ligands (Scheme 21).[62] An interesting feature of the Pd_3 cluster is its ability to act as an electron reservoir, in addition to containing NO ligands that are incorporated into valuable organic products.



Scheme 21. $[Pd_3(NO)_2(\mu\text{-}OCOCF_3)_4(\eta^2\text{-}C_6H_5Me)_2]$ as a validated precursor to biphenyls, diarylamines, and carbazoles.

4. Summary and Outlook

NO_x ligands are redox-active participants in oxidative processes involving Pd and a range of organic substrates, particularly aromatics and alkenes, but also alkanes. The resurgence of interest in the redox properties of NO_x ligands indicates that the design of Pd catalysts could benefit from the inclusion of such ligands within the coordination sphere at Pd. Moreover, much of the recent work builds on the foundations laid within the literature, going as far back as the late 1960s.

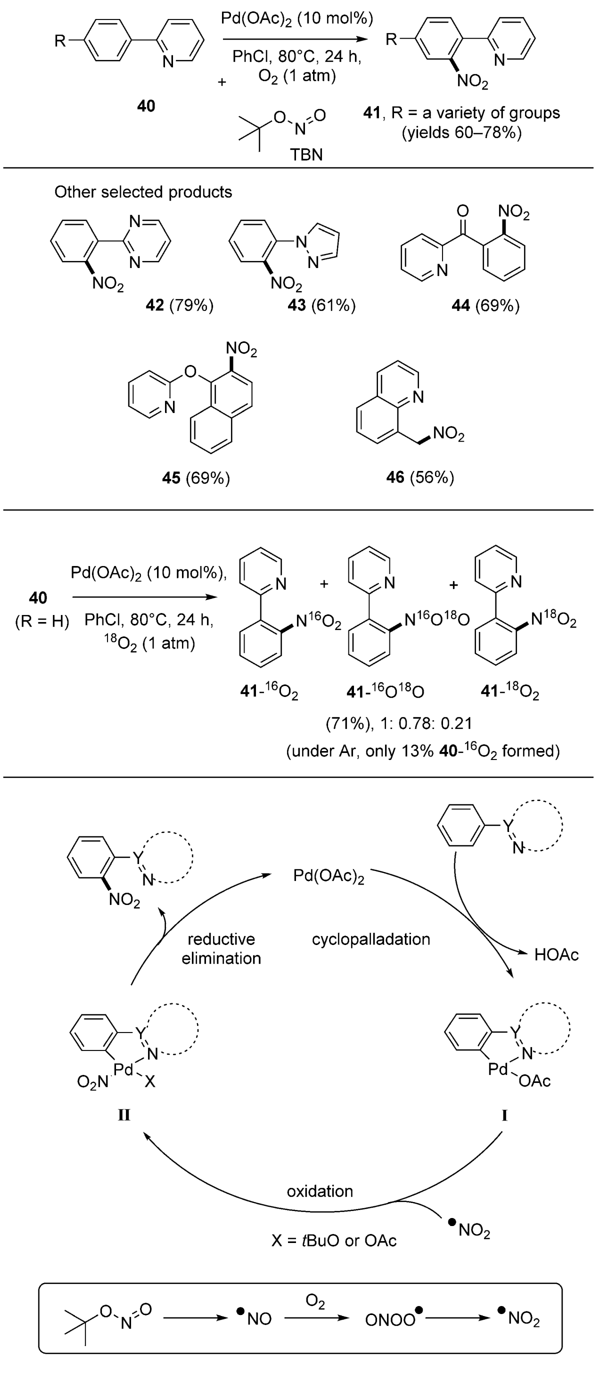
For the field it is important that the roles of NO, NO_2, NO_2^-, and NO_3^- are fully examined under the differing catalytic conditions, particularly for the reactions detailed in this Minireview. Learning from the work conducted in biochemistry may prove useful in this respect.[63]

The precise role of MNO_3 and/or MNO_2 at Pd, particularly when included as additives for reactions, remains unclear. Are NO_3/NO_2 critical ligands (pseudohalides) at Pd under working catalyst conditions? And, if $Pd–NO_3/Pd–NO_2$ species are present, then C–O or C–X bond formation must be favored over C–N bond formation in certain acetoxylation processes, for example. The reasons for this preference are currently less clear, especially as NO_2 anions can reductively eliminate at Pd, including in Pd species with higher oxidation states.[64] Moreover, as stated earlier, Cámpora et al. showed that Pd–NO adducts can be characterized.[21]

Building on the historical work of Tisue,[17] Norman,[18,19] and their co-workers (as outlined in Section 1), catalytic aromatic nitration is feasible using both removable[65] and nonremovable[66] directing groups at Pd in the presence of MNO_2 salts, which is in keeping with nitration chemistry at Pd^{II}, requiring a special phosphine ligand to induce reductive elimination.[67] The very recent work of Ranu,[68] Jiao,[69] and their co-workers is particularly remarkable in that catalytic aromatic nitration is feasible using *tert*-butyl nitrite (TBN) with molecular O_2. A series of different substrates containing a range of directing groups affected the nitration of $C(sp^2)–H$ bonds, affording products such **41–45**. Furthermore, the $C(sp^3)–H$ bond activation gave **46**, a substrate that was also acetoxylated in Sanford’s NO_x redox chemistry.[1]

From a mechanistic perspective, Jiao showed that isotopically labeled O_2 was found in the organic products. The TBN generates ·NO radicals in situ, which react with molecular O_2 and C–H substrates, mediated at Pd (as outlined in Scheme 22). The catalytic cycle involves cyclopalladation (giving **I**) and oxidation with $\cdot NO_2$ to give **II**, which reductively eliminates to give the nitrated aromatic product and regenerates the catalyst. Jiao’s mechanistic work is complemented by that previously reported by Sun and co-workers, who showed that $\cdot NO_2$ mediates the *ortho* nitration of azoarenes with catalytic $Pd(OAc)_2$ in dichloroethane at 90 °C.[70] The aromatic nitration methodologies could thus find broader synthetic application.

The recent work by Grubbs[2] on the aldehyde-selective Wacker oxidation of terminal alkenes is a significant breakthrough, particularly with regard to the development of synthetic methodology. The earlier work of Feringa[29] arguably underpins these studies, particularly with regard to reaction feasibility and the proposal of bimetallic catalyst species. Further corroboration of the latter proposal has been made by computation (DFT methods), although experimental details are still needed for support (e.g. order in Pd and Cu).[31] It is also important to acknowledge the contributions



Scheme 22. Jiao's recent work on the catalytic nitration of C(sp^2)−H and C(sp^3)−H bonds. The bond highlighted in bold shows the position of the new nitro group. The catalytic cycle is drawn as reported in the original paper.[69] The inset at the bottom shows the degradation of TBN to NO and then the reoxidation to give NO_2 in situ.

made by Wenzel[30] and Andrews[9,10,12] on catalytic redox processes involving NO_x.

It is evident from the research described in this Minireview that redox-active NO_x ligands can act as high-energy stoichiometric oxidants in Pd-mediated reactions, operating catalytically in the presence of a terminal oxidant, such as air/O_2. Presumably, an extension to other transition metals can be anticipated, especially as NO_x ligands are ubiquitous in many transition-metal complexes. The involvement of NO_2 at Cu in Wacker oxidations is intriguing.[2] The true test for the chemistry described here will come in the target-orientated synthesis of more complex synthetic targets, such as natural products, medicinal agents, and advanced materials. Further mechanistic and experimental evidence is needed, but it is clear that we are seeing a renaissance in NO_x redox chemistry, and certainly new synthetic methodologies are anticipated within the next few years.

Acknowledgement

Dr. J. M. Lynam (York) is thanked for many discussions concerning the role of nitrate and nitrite in Pd-mediated organic transformations. Dr. M. Wenzel is acknowledged for crystallizing [$Pd_3(OAc)_6$] and Dr. A. C. Whitwood for the X-ray diffraction analysis. I am very grateful to the reviewers of this manuscript for their constructive and critical comments. The research leading to some of these results has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115360 (Chem21), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. The EPSRC, the University of York, and the Wild fund have supported previous studies relating to some of the chemistry described in this Minireview. I am grateful to the University of York Library staff, in particular to Margaret Dillon, for locating less-accessible research articles cited within this Minireview. From a personal perspective, examining the electrophilic substitution of aromatic compounds with Pd^{II} nitrate salts, reported by Norman, Thomas, and co-workers in York,[18,19] has been a real delight.

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[1] K. J. Stowers, A. Kubota, M. S. Sanford, *Chem. Sci.* **2012**, *3*, 3192–3195.
[2] a) Z. K. Wickens, B. Morandi, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2013**, *52*, 11257–11260; *Angew. Chem.* **2013**, *125*, 11467–11470; b) Z. K. Wickens, K. Skakuj, B. Morandi, R. H. Grubbs, *J. Am. Chem. Soc.* **2014**, *136*, 890–893.
[3] C. E. Housecroft, E. C. Constable in *Chemistry, 2nd ed.*, Pearson Education, Harlow, **2002**, Chap. 21, pp. 637–644.
[4] P. A. Chaloner in *Handbook of Coordination Catalysis in Organic Chemistry*, Butterworth, Chicago, **1986**, pp. 535–536.
[5] M. Tamura, T. Yasui, *Chem. Commun.* **1968**, 1209–1209.
[6] N. I. Kuznetsova, V. A. Likholobov, M. A. Fedotov, Y. I. Yerrnakov, *React. Kinet. Catal. Lett.* **1979**, *12*, 235–239.
[7] N. I. Kuznetsova, V. A. Likholobov, M. A. Fedotov, Y. I. Yerrnakov, *J. Chem. Soc. Chem. Commun.* **1982**, 973–974.
[8] J. E. Bäckvall, A. Heumann, *J. Am. Chem. Soc.* **1986**, *108*, 7107–7110.
[9] M. A. Andrews, K. P. Kelly, *J. Am. Chem. Soc.* **1981**, *103*, 2894–2896.
[10] M. A. Andrews, C. W. F. Cheng, *J. Am. Chem. Soc.* **1982**, *104*, 4268–4270.
[11] A. Heumann, F. Chauvet, B. Waegell, *Tetrahedron Lett.* **1982**, *23*, 2767–2768.

[12] M. A. Andrews, T. C. T. Chang, C. W. F. Cheng, *Organometallics* **1985**, *4*, 268 – 274.

[13] F. Mares, S. E. Diamond, F. J. Regina, J. P. Solar, *J. Am. Chem. Soc.* **1985**, *107*, 3545 – 3552.

[14] R. B. Woodward, F. V. Brutcher, Jr., *J. Am. Chem. Soc.* **1958**, *80*, 209 – 211.

[15] K. Ichikawa, S. Uemura, T. Okada, *Nippon Kagaku Zasshi* **1969**, *90*, 212 – 218.

[16] P. M. Henry, *J. Org. Chem.* **1971**, *36*, 1886 – 1890.

[17] T. Tisue, W. J. Downs, *J. Chem. Soc. D* **1969**, 410a.

[18] R. O. C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1974**, 369 – 372.

[19] F. R. S. Clark, R. O. C. Norman, C. B. Thomas, J. S. Willson, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1289 – 1294.

[20] S. L. Zultanski, S. S. Stahl, *J. Organomet. Chem.* **2015**, DOI: 10.1016/j.jorganchem.2015.03.003.

[21] J. Cámpora, P. Palma, D. Del Rio, E. Carmona, C. Graiff, A. Tiripicchio, *Organometallics* **2003**, *22*, 3345 – 3347.

[22] N. I. Kuznetsova, V. A. Likholobov, Y. I. Yerrnakov, *React. Kinet. Catal. Lett.* **1983**, *22*, 139 – 142.

[23] S.-J. Lou, D.-Q. Xu, Z.-Y. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10330 – 10335; *Angew. Chem.* **2014**, *126*, 10498 – 10503.

[24] P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824 – 889.

[25] C. Amatore, A. Jutand, *Coord. Chem. Rev.* **1998**, *178*, 511 – 528, and references therein.

[26] L. Firmansjah, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 11340 – 11341.

[27] I. J. S. Fairlamb, *Org. Biomol. Chem.* **2008**, *6*, 3645 – 3656.

[28] For a general recent review examining the use of ESI-MS in homogeneous catalysis, see: K. L. Vikse, Z. Ahmadi, J. S. McIndoe, *Coord. Chem. Rev.* **2014**, *279*, 96 – 114.

[29] B. L. Feringa, *J. Chem. Soc. Chem. Commun.* **1986**, 909 – 910.

[30] T. T. Wenzel, *J. Chem. Soc. Chem. Commun.* **1989**, 932 – 933.

[31] Y. Y. Jiang, Q. Zhang, H. Z. Yu, Y. Fu, *ACS Catal.* **2015**, *5*, 1414 – 1423.

[32] For kinetic studies on an exemplary Sonogashira alkynylation reaction involving Pd and Cu, see: C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 2053 – 2064.

[33] Z. K. Wickens, P. E. Guzmán, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2015**, *54*, 236 – 240; *Angew. Chem.* **2015**, *127*, 238 – 242.

[34] For an examination of the interactions of NO, nitrite, and hyponitrite with iron porphyrins and their role in the linkage isomerization in Heme-NO_x ($x = 1$ or 2) compounds, see: N. Xu, J. Yi, G. B. Richter-Addo, *Inorg. Chem.* **2010**, *49*, 6253 – 6266.

[35] For leading reviews, see: a) L. E. Hatcher, P. R. Raithby, *Coord. Chem. Rev.* **2014**, *227 – 278*, 69 – 79; b) J. L. Burmeister, *Coord. Chem. Rev.* **1968**, *3*, 225 – 245.

[36] "Comprehensive Coordination Chemistry II": *Fundamentals*: *Ligands*, *Complexes*, *Synthesis Purification*, *and Structure*, *Vol. 1* (Eds.: J. A. McCleverty, T. J. Meyer), Elsevier, Amsterdam, **2003**.

[37] M. A. Hitchman, G. L. Rowbottom, *Coord. Chem. Rev.* **1982**, *42*, 55 – 132.

[38] J. L. Burmeister, *Coord. Chem. Rev.* **1968**, *3*, 225 – 245.

[39] S. E. Bajwa, T. E. Storr, L. E. Hatcher, T. J. Williams, C. G. Baumann, A. C. Whitwood, D. R. Allan, S. J. Teat, P. R. Raithby, I. J. S. Fairlamb, *Chem. Sci.* **2012**, *3*, 1656 – 1661.

[40] a) M. Nonoyama, *Synth. React. Inorg. Met.-Org. Chem.* **1999**, *29*, 119 – 124; b) M. Nonoyama, K. Nakajima, *Polyhedron* **1998**, *18*, 533 – 543.

[41] For a summary of several organometallic transformations, of relevance to synthesis and catalysis, which have been studied in the solid state, see the following review: S. D. Pike, A. S. Weller, *Philos. Trans. R. Soc. London Ser. A* **2015**, *373*, 20140187.

[42] An *exo* "Ni-ON=O" group has been observed in [Ni(Et_4dien)(η^2-O,ON)(η^1-NO_2)]. See: a) L. E. Hatcher, J. Christensen, M. L. Hamilton, J. Trincao, D. R. Allan, M. R. Warren, I. P. Clarke, M. Towrie, D. S. Fuertes, C. C. Wilson, C. H. Woodall, P. R. Raithby, *Chem. Eur. J.* **2014**, *20*, 3128 – 3134.

[43] M. R. Warren, S. K. Brayshaw, L. E. Hatcher, A. L. Johnson, S. Schiffers, A. J. Warren, C. H. Woodall, P. R. Raithby, S. J. Teat, J. E. Warren, *Dalton Trans.* **2012**, *41*, 13173 – 13179.

[44] a) J. L. Burmeister, R. C. Timmer, *J. Inorg. Nucl. Chem.* **1966**, *28*, 1973 – 1978; b) M. Mares, D. A. Palmer, H. Kelm, *Inorg. Chim. Acta* **1978**, *27*, 153 – 156.

[45] T. E. Storr, C. G. Baumann, R. J. Thatcher, S. De Ornellas, A. C. Whitwood, I. J. S. Fairlamb, *J. Org. Chem.* **2009**, *74*, 5810 – 5821.

[46] CCDC 1036477 ([$Pd_3(OAc)_6 \cdot H_2O$]) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif). Formula: $C_{12}H_{18}O_{12}Pd_3 \cdot 0.21(H_2O)$; unit cell parameters: *a* 8.17659(14) *b* 29.3419(4) *c* 16.6152(3), *P*21/*n* (space group).

[47] For details on the decomposition of $Pd(OAc)_2$ in protic solvents, of relevance to Suzuki – Miyaura cross-coupling, see: L. A. Adrio, B. N. Nguyen, G. Guilera, A. G. Livingston, K. K. Hii, *Catal. Sci. Technol.* **2012**, *2*, 316 – 323.

[48] V. I. Bakhmutov, J. F. Berry, F. A. Cotton, S. Ibragimov, C. A. Murillo, *Dalton Trans.* **2005**, 1989 – 1992.

[49] I. P. Stolyarov, L. I. Demina, N. V. Cherkashina, *Russ. J. Inorg. Chem.* **2011**, *56*, 1532 – 1537.

[50] a) S. S. Zalesskiy, V. P. Ananikov, *Organometallics* **2012**, *31*, 2302 – 2309; b) A. R. Kapdi, A. C. Whitwood, D. C. Williamson, J. M. Lynam, M. J. Burns, T. J. Williams, A. J. Reay, J. Holmes, I. J. S. Fairlamb, *J. Am. Chem. Soc.* **2013**, *135*, 8388 – 8399.

[51] M. Cong, Y. Fan, J.-M. Raimundo, J. Tang, L. Peng, *Org. Lett.* **2014**, *16*, 4074 – 4077.

[52] R. B. Bedford, J. G. Bowen, R. B. Davidson, M. F. Haddow, A. E. Seymour-Julen, H. A. Sparkes, R. L. Webster, *Angew. Chem. Int. Ed.* **2015**, *54*, 6591 – 6594; *Angew. Chem.* **2015**, *127*, 6691 – 6694.

[53] N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972 – 4973. Also, see: C. G. Baumann, S. De Ornellas, J. P. Reeds, T. E. Storr, T. J. Williams, I. J. S. Fairlamb, *Tetrahedron* **2014**, *70*, 6174 – 6187.

[54] B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885 – 898.

[55] E. Gretz, T. F. Oliver, A. Sen, *J. Am. Chem. Soc.* **1987**, *109*, 8109 – 8110.

[56] A. Sen, E. Gretz, T. F. Oliver, Z. Jiang, *New J. Chem.* **1989**, *13*, 755 – 760.

[57] A. Sen, *Platinum Met. Rev.* **1991**, *35*, 126 – 132.

[58] L.-C. Kao, A. C. Hutson, A. Sen, *J. Am. Chem. Soc.* **1991**, *113*, 700 – 702.

[59] M. N. Vargaftik, I. P. Stolarov, I. I. Moiseev, *J. Chem. Soc. Chem. Commun.* **1990**, 1049 – 1050.

[60] English translation, see: I. P. Stolyarov, M. N. Vargaftik, I. I. Moiseev, *Kinet. Katal.* **1989**, *30*, 1513 – 1513.

[61] Z. An, X. Pan, X. Liu, X. Han, X, Bao, *J. Am. Chem. Soc.* **2006**, *128*, 16028 – 16029.

[62] R. E. Podobedov, T. A. Stromnova, I. P. Stolyarov, *Russ. Chem. Bull. Int. Ed.* **2010**, *59*, 473 – 475.

[63] M. D. Bartberger, W. Liu, E. Ford, K. M. Miranda, C. Switzer, J. M. Fukuto, P. J. Farmer, D. A. Wink, K. N. Houk, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10958 – 10963.

[64] For examples of the reductive elimination of a nitro group from Pd^{IV} species, see: a) B. Majhi, D. Kundu, S. Ahammed, B. C. Ranu, *Chem. Eur. J.* **2014**, *20*, 9862 – 9866 (using *t*BuONO); b) J. Dong, B. Jin, P. Sun, *Org. Lett.* **2014**, *16*, 4540 – 4542 (using NO_2).

[65] W. Zhang, J. Zhang, S. Ren, Y. Liu, *J. Org. Chem.* **2014**, *79*, 11508 – 11516.

[66] W. Zhang, S. Lou, Y. Liu, Z. Xu, *J. Org. Chem.* **2013**, *78*, 5932 – 5948.

[67] B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898–12899.

[68] B. Majhi, D. Kundu, S. Ahammed, B. C. Ranu, *Chem. Eur. J.* **2014**, *20*, 9862–9866.

[69] Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng, N. Jiao, *ACS Catal.* **2015**, *5*, 1956–1963.

[70] J. Dong, B. Jin, P. Sun, *Org. Lett.* **2014**, *16*, 4540–4542.

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